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10/553,320	11/03/2005	Yoshiko Takayama	2005_1592A	1755

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EXAMINER	
HUANG, GIGI GEORGIANA	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
10/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,320	TAKAYAMA ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-20* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/16/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The response filed July 16, 2009 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claims 13-16 have been amended.

   b. Claim 17-20 has been added.

2. Claims 13-20 are pending in the case. Newly added claims 18-20 are withdrawn as they are directed to the non-elected invention.

3. Claims 13 and 17 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

6. New grounds of rejection are set forth in the current office action.

New Grounds of Rejection

7. Due to the amendment of the claims the new grounds of rejection are applied:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The term “Rho kinase inhibitor” is not defined and it does not address the amount of binding desired for the receptors, nor the degree of inhibition for the claimed method, and the compounds that would accomplish this for the claimed method other than fasudil hydrochloride, etacrynic acid and 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid, 2-chloro-6,7-dimethoxy-N-[5-1H-indazolyl]quinazoline-4-amine, N-(1-benzyl-4-piperidinyl)-1H-indazole-5-amine dihydrochloride monohydrate , and C3 enzyme (Exoenzyme C3 or C3 ADP-ribosyltransferase) which is disclosed in the specification.

The term “Rho kinase inhibitor " is not adequately described as it is defined by a functional characteristic where it is defined by what it *does* and not what it *is*. Second, it does not describe adequately the degree of access, binding, or degree of inhibition to ascertain what compounds would fulfill the description. As a result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

There is also no specific structure/function relationship taught in the reference to drawn from as the specific compounds disclosed have different cores with no specific relationship to the function recited in the claims. The claims with the term also encompass compounds yet to be found whereby Applicant would not be in possession of all the compounds embraced by the term. McKerracher et al. (U.S. Pat. Pub. 2008/0233098) teaches screening assays to identify Rho antagonists (inhibitors) such as Rho-kinase inhibitors (Paragraph 16-23, 44-50), and Dole et al. (U.S. Pat. Pub.

2005/0014783) teaches identification of Rho-kinase inhibitor compounds with assays known in the art and the compounds with an IC_{50} of 10uM are considered effective (paragraph 88), which are after the filing date of the instant application. Thereby, while having written description fasudil hydrochloride, etacrynic acid and 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid, 2-chloro-6,7-dimethoxy-N-[5-1H-indazolyl]quinazoline-4-amine, N-(1-benzyl-4-piperidinyl)-1H-indazole-5-amine dihydrochloride monohydrate , and C3 enzyme, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is directed to Exoenzyme C3 or a ROCK inhibitor but as addressed by Applicant, Exoenzyme C3 is ROCK-I inhibitor as it abolishes the ROCK-I activation. It is unclear what the distinction is between the term and Exoenzyme C3 or if one is encompassed by the other. It does not allow one of skill in the art to ascertain the metes and bounds of the invention. For purposes of expediting prosecution, Exoenzyme C3 is treated as being encompassed by the ROCK inhibitor.

10. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. The claim is dependent from claim 13 and directed to where the ROCK inhibitor of claim 13 is selected from the group consisting of 2-chloro-6,7-dimethoxy-N-[5-1H-indazolyl]quinazoline-4-amine, N-(1 -benzyl-4-piperidinyl)- 1H-indazole-5-amine dihydrochloride, 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid and fasudil hydrochloride. It is unclear from the way the claim currently is written if Exoenzyme C3 is still present in the claim as an alternative as claim 17 does not state that the drug for the method is a ROCK inhibitor selected from the group consisting of 2-chloro-6,7-dimethoxy-N-[5-1H-indazolyl]quinazoline-4-amine, N-(1 -benzyl-4-piperidinyl)- 1H-indazole-5-amine dihydrochloride, 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid and fasudil hydrochloride. It is also confusing as Exoenzyme C3 is ROCK-I inhibitor as addressed above. It does not allow one of skill in the art to ascertain the metes and bounds of the invention. For purposes of expediting prosecution, the claim is treated as reciting that the drug for the method is a ROCK inhibitor selected from the group consisting of 2-chloro-6,7-dimethoxy-N-[5-1H-indazolyl]quinazoline-4-amine, N-(1 -benzyl-4-piperidinyl)- 1H-indazole-5-amine dihydrochloride, 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid and fasudil hydrochloride.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (WO 03/020281) in view of Lehmann et al (Inactivation of Rho Signaling Pathway Promotes CNS Axon Regeneration).

Hellberg et al. teaches the use of compounds that promote neuron regeneration or neurite outgrowth for the treatment of conditions such as dry eye and other conditions related to corneal nerve damage (e.g. corneal sensitivity after LASIK). The compounds are neurotrophic and are used promote neurite outgrowth or regenerate severed neurons, examples include bFGF(basic fibroblast growth factor), NGF (Nerve growth factor), neotrofin, idebenone, and clenbuternol (see full document, specifically Abstract, Page 4 line 16-Page 5 line 25, Page 6 line 12-23, Claim 1-4, 7-10, 13-16).

Hellberg et al. do not expressly teach the use of Rho kinase inhibitors such as C3.

Lehmann et al. teaches that Rho inhibition fostered regeneration of neurons and yielded extended neurites. Lehmann teaches that in vitro test showed that C3 affected the growth of neurites from retinal cells and in vivo Lehmann tested optic nerves with C3 transferease (C3 enzyme) showing that the transected axons fostered extension and regeneration.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize a Rho inhibitor that promotes neuron regeneration or neurite outgrowth for corneal injury, as suggested by Lehmann, and produce the instant invention. It would be obvious for one of skill in the art to use another neurite

promoter such as C3 taught by Lehmann for corneal injury as Hellberg et al. teaches the use of compounds that promote neuron regeneration or neurite outgrowth for corneal disorders and it is obvious to use a known neurite/neuron promoter for a known purpose for neurite/neuron promoters for a specific treatment. Absent evidence to the contrary, neurite promotion of nerves cells is applicable to all neurons and would function in any neuron as they all have the same cellular structure (soma, dendrite, nucleus, node of Ranvier, Schwann cell, myelin sheath, axon) and function (synaptic transmission).

One of ordinary skill in the art would have been motivated to do this because it is desirable to use a known compound such as C3 (Rho kinase inhibitor) with known properties for promoting axon extension and regeneration in vivo in the eye, to be used for a known purpose (neurite/neuron promoters for corneal disorders) which utilizes compounds that promotes neuron regeneration or neurite outgrowth, as it is desirable to have different compounds useful for the same purpose and to have new methods of treatment for a known compound which allows for new sales.

12. Claims 13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (WO 03/020281) in view of Hara et al. (Protein kinase inhibition by fasudil hydrochloride promotes neurological recovery after spinal cord injury in rats).

Hellberg et al. teaches the use of compounds that promote neuron regeneration or neurite outgrowth for the treatment of conditions such as dry eye and other conditions related to corneal nerve damage (e.g. corneal sensitivity after LASIK). The compounds are neurotrophic factors and are used promote neurite outgrowth or regenerate

severed neurons, examples include bFGF(basic fibroblast growth factor), NGF (Nerve growth factor), neotrofin, idebenone, and clenbuternol (see full document, specifically Abstract, Page 4 line 16-Page 5 line 25, Page 6 line 12-23, Claim 1-4, 7-10, 13-16).

Hellberg et al. do not expressly teach the use of Rho kinase inhibitors such as fasudil hydrochloride.

Hara et al. teaches that fasudil hydrochloride (HA1077) can promote neurological recovery after traumatic spinal cord injuries (SCI) as are other agents such as neurotrophic factors known in the art that improve neurological recovery in SCI (Introduction-Page 94, e.g. basic fibroblast growth factor-citation 5, Nerve growth factor-citation 16, 31, 44,) .

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize fasudil hydrochloride to promote neuron regeneration or neurite outgrowth for corneal injury, as suggested by Hara, and produce the instant invention. It would be obvious for one of skill in the art to use another neurite promoter such as fasudil for corneal injury as Hellberg et al. teaches the use of compounds such as neurotrophic factors to promote neuron regeneration or neurite outgrowth for corneal disorders and Hara et al. teaches that neurotrophic factors and fasudil are both functionally useful (functionally equivalent) for the same condition (neurological recovery for spinal cord injuries), wherein it would be obvious to use fasudil for the same methods of neural recovery as neurotrophic factors such as corneal nerve damage as taught by Hellberg with a reasonable expectation of success. It is obvious to one of skill in the art to utilize a known neurite/neuron promoter (fasudil) for

the same purpose as similar neurite/neuron promoters (neurotrophic factors) for a specific treatment (corneal nerve damage) when they have both been effective for a similar conditions and/or therapeutic result (neurological recovery of spinal cord injuries).

One of ordinary skill in the art would have been motivated to do this because it is desirable to use a known compound such as fasudil hydrochloride with known properties for promoting axon extension and regeneration, to treat the same conditions as another neurite/neuron promoters such as neurotrophic factors (e.g. bFGF, NGF) when it is they are both effective to treat neurological damage. It is also is desirable to have different compounds useful for the same purpose and to have new methods of treatment for a known compound which allows for new sales.

Double Patenting

13. Claim 13 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19-27 of U.S. Patent No. 7485654. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the broader instant claim as the patented compound is a ROCK inhibitor.

Response to Arguments

14. The information disclosure statement filed 1/13/2006 has been reconsidered and the IDS submitted 7/16/2009 with the references are attached to the current action.

15. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (WO 03/020281) in view of Lehmann et al (Inactivation of Rho Signaling Pathway Promotes CNS Axon Regeneration).

Applicant's arguments filed 7/16/2009 have been fully considered but they are not persuasive. Applicant asserts that the optic nerve testing in Lehmann is different form the nerves of the cornea which is different from the optic nerve. It is noted that Applicant uses the term “ophthalmic nerve” which is taken to mean the optic nerve but is confusing as it is the ophthalmic nerve branch of cranial nerve V that innervates the cornea. Applicant states that the function, origin, and destinations of the two are different wherein one of ordinary skill in the art would not expect a substance having neuritogenesis action in the optic nerve would have similar effects in corneal nerves. The argument have been considered but are not persuasive as while cranial nerve II and V have different destinations, they have the same primary origin being derived from ectoderm verses the rest of the PNS. Additionally, Lehmann tests retinal ganglion cells and the optic nerve which are also sensory like the corneal nerves (same function). The neurons have the same cellular construct (e.g. dendrite, axon) with the same function of signal transduction wherein neurite promotion of nerves cells by C3 would be applicable to all neurons and would be expected to function the same in any neuron absent evidence to the contrary. It would also be obvious to one of skill in the art as the teachings of Lehmann are not only to the optic nerve but also to retinal cells with neuritogenesis and there is a known association of retinopathy and corneal sensitivity

(see Mittal S. et al.) wherein it would be obvious to one of skill in the art that the teachings would also apply to corneal nerves.

Accordingly, the rejection is maintained.

16. Claim 13 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19-27 of U.S. Patent No. 7485654.

There is an obvious typographical error as addressed by Applicant which is appreciated and the claims of the Patent addressed are indeed 1-3. The rejection line now: Claim 13 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-3 of U.S. Patent No. 7485654

Applicant's arguments filed 7/16/2009 have been fully considered but they are not persuasive. Applicant asserts that the claims are limited to 4 compounds which is presented in claim 17 but is not commensurate in scope with claim 13 which is directed to ROCK inhibitors and the patented claims described a ROCK inhibitor.

Accordingly, the rejection is maintained.

Conclusion

17. Claims 13 and 17 are rejected.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612